UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,507	01/23/2004	Bruce R. Line	Franco-Line Microprtcles	5234

50438 7590 03/03/2010

JUNEAU PARTNERS
333 N Fairfax St.
Suite 305
ALEXANDRIA, VA 22301

EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
03/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,507	LINE ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/23/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,11-15,17,20,25-71 and 82-95* is/are pending in the application.

4a) Of the above claim(s) *27,28,41-71 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,11-15,17,20,25,26,29-40 and 85-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 11/23/2009, in reply to the Office Action mailed 7/10/2009, is acknowledged and has been entered. Claims 1, 8, 11-15, 17, 20, 25, 26, 29-41, 85 and 86 have been amended. Claims 87-95 have been added. Claims 1, 8, 11-15, 17, 20, 25-71 and 82-95 are pending, of which claims 27, 28, 41-71 and 82-84 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1, 8, 11-15, 17, 20, 25, 26, 29-40 and 85-95 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

New Grounds for Rejection

Claim Objections

Claim 87 is objected to because of the following minor informalities: the claim lacks punctuation at the end of the sentence. In addition, the claim recites several radionuclides in duplicate. For example At-211 appears on both lines 5 and 6 of the claim; I-123 appears on both lines 6 and 8, Sm-153 appears on both lines 6 and 8, Gd-

159 appears on both lines 7 and 8, etc. for multiple other instances of other radionuclides. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, 11-15, 17, 20, 25, 26, 29-34, 85-90, 92 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The independent claim is drawn to a combination therapeutic and diagnostic radiopharmaceutical microparticle comprising a non-radioactive core. However, lines 5-7 of claim 1 recite that a terminal functional group is "attached to a chelated radiopharmaceutical agent, said chelated radiopharmaceutical agent is selected from the group consisting of a chelated beta-emitting therapeutic radionuclide and a chelated gamma-emitting diagnostic radionuclide. The claims are confusing because the preamble recites a combination therapeutic and diagnostic radiopharmaceutical microparticle, while the Markush terminology of the claim indicates that the identity of the radionuclide as therapeutic or diagnostic is presented in the alternative. See MPEP 2173.05(h). Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex*

parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925). In the instant case, it is unclear whether or not the claim intends for the therapeutic and diagnostic radionuclides to be presented in the alternative, since the preamble of the claim recites a combination therapeutic and diagnostic radiopharmaceutical microparticle.

For the purpose of prior art search, the examiner has construed the therapeutic and diagnostic radionuclides to be present in the alternative in order to give weight to the text of the body of the claim, rather than the preamble of the claim.

Claims 8, 11-15, 17, 20, 25, 26, 29-34, 36-40, 85-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 is drawn to the radiopharmaceutical microparticle of claim 1, further comprising wherein said therapeutic beta-emitting radionuclide is Yttrium-90. The claim is confusing because the limitation "further comprising" indicates that the composition comprises an additional ingredient that was not present in the independent claim, however the limitation "said therapeutic beta-emitting radionuclide is yttrium-90" indicates that the radionuclide is identifying the radionuclide of claim 1 more specifically, due to use of the term "said," which implies antecedent basis from claim 1. See MPEP 2173. Clarification is requested. Claims 11-15, 17, 20, 25, 26, 29-34, 36-40, 85-93 feature similar "further comprising wherein said language" to that of claim 8, which is unconventional and confusing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 12-14, 17, 25, 26, 29-34, 85, 86, 90, 92 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al.* (*Magnetic Resonance in Medicine*, 2001, 46, p. 781–788) in view of Domb *et al.* (US 5,578,325).

Kobayashi discloses that macromolecules conjugated with polyethylene glycol (PEG) acquire more hydrophilicity, resulting in a longer half-life in circulation and lower immunogenicity. Two novel conjugates for MRI contrast agents were synthesized from a generation-4 polyamidoamine dendrimer (G4D), 2-(*p*-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (1B4M), and one or two PEG molecules with a molecular weight of 20000 Da (PEG_2-G4D-(1B4M-Gd)$_{62}$ (MW: 96 kD), PEG_1-G4D-(1B4M-Gd)$_{63}$ (MW: 77 kD)). Although the blood clearance was slower, PEG_2-G4D-(1B4M-Gd)$_{62}$ was excreted more readily without renal retention than the other two

preparations. In conclusion, the positive effects of PEG conjugation on a macromolecular MRI contrast agent were found to be prolonged retention in the circulation, increased excretion, and decreased accumulation in the organs (abstract). ^{153}Gd-Labeled PEG-Conjugated G4D-(1B4M)x was prepared (page 787).

Kobayashi does not specifically recite the size of the PEG-conjugated G4D-(1B4M)x conjugates, such that PEG is in the form of a micropartice.

Domb discloses injectable particles that are not rapidly cleared from the bloodstream by macrophages of the reticuloendothelial system (abstract). Nonlinear block copolymers containing one or more hydrophilic polymers and one or more hydrophobic bioerodible polymers are prepared. The hydrophilic polymer may be PEG, the hydrophobic polymer may be polylactic acid, polyphosphazenes, etc. Ligands can be attached to one or more polymer chains to achieve a variety of properties for a variety of applications (column 2, lines 46+). Materials incorporated onto or within the polymers include biologically active materials such as antibodies, etc. (column 3, lines 14 – 23). Microparticles can be prepared by forming the block copolymers in sizes ranging from 1 – 1000 micron (column 9, line 53 – column 10, line 43). See column 12 and also Example 21. Indium-111 can be directly attached to the multiblock copolymer by complex formation via DTPA. Regarding claims 31 and 32, it is noted that the functional recitation that the particle has the claimed density range is not given patentable weight to distinguish over Burns. "Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical

structure or composition as that which is claimed, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Since Domb discloses microspheres comprising the same polymers as those claimed, they would inherently be capable of having the same density. Lyophilized particles are disclosed, as are carriers, adjuvants etc. (column 3, line 30).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the conjugation of dendrimer-chelate-radionuclide moieties of Kobayashi onto microspheres, such as PEG-containing microspheres disclosed in Domb. One would have been motivated to do so because both Kobayashi and Domb are directed to providing diagnostic imaging agents in a form which is not rapidly cleared from the blood stream or providing longer half life (see abstacts of both Domb and Kobayashi). Biodistribution studies show injectable partices have a prolonged half-life in blood compared to particles not containing poly(alkylene glycol) on their surface. One would have had a reasonable expectation of success in doing so because Kobayashi discloses methods of conjugation of dendrimer to PEG polymer, as set forth above.

Claims 1, 8, 11-15, 17, 25, 26, 29-40 and 85-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al.* (*Magnetic Resonance in Medicine*, 2001, 46, p. 781–788) in view of Domb *et al.* (US 5,578,325), further in view of Watson (US 5,914,095).

The rejection over Kobayasi in view of Domb is applied as above.

Watson teaches polychelants and their metal chelates which are useful in diagnostic imaging and in radiotherapy and which comprise a plurality of macrocyclic chelant moieties, e.g. DOTA residues, conjugated to a dendritic polyamine backbone molecule, e.g. a starburst dendrimer (abstract). The compounds are useful in X-ray and MRI image enhancement, as well as therapeutic and diagnostic nuclear medicine. One class of these novel compounds is composed of a dendrimer, preferably a starburst dendrimer backbone molecule to which a multiplicity of macrocyclic chelant moieties are attached. These polychelant compounds and the chelates and salts thereof are here termed magnifiers. The chelant moieties in the magnifiers are capable of chelating metal ions with a high level of stability, and are metallated with the appropriate metal ion(s) to enhance images and/or to deliver cytotoxic doses of radioactivity. Suitable dendrimers include PAMAM, etc.; suitable chelators include DOTA, DTPA, etc. (column 7-9). Particularly preferred radiisotopes of some of the foregoing include ^{90}Y, ^{99m}Tc, ^{111}In, etc. (column 11). Conjugation to polymer is disclosed.

It would have been obvious to one of ordinary skill in the art the time of the invention to substitute one known metal chelator for another, such as substitution of DOTA as a functional equivalent for DTPA in the conjugates of Kobashi and/or Domb, when the teaching of Kobashi and Domb are taken in view of Watson. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of

obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (DTPA and DOTA) and their functions were known in the art at the time of the instant invention as metal chelators for chelating radionuclides or paramagnetic metal ions for diagnostic applications in MRI or scintigraphic imaging. One of ordinary skill in the art could have substituted one known chelator for another, and the results of the substitution would have been predictable. Likewise, one could have substituted one known radionuclide for another. For example, Watson teaches that dendrimer-chelate conjugates can used to chelate either paramagnetic ions for use in MRI, or radionuclide such as ^{90}Y and/or ^{111}In for scintigraphic imaging.

Claims 1, 8, 11-15, 20, 17, 25, 26, 29-40 and 85-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi *et al.* (*Magnetic Resonance in Medicine*, 2001, 46, p. 781–788) and Domb *et al.* (US 5,578,325), in view of Watson (US 5,914,095), further in view of Danthi *et al.* (US 2003/0133972)

The rejection over Kobayashi and Domb in view of Watson is applied as above.

Danthi teaches that dendrimers can be readily used as linking carriers by employing a variety of chemical conjugation techniques to attach the targeting entity and therapeutic entity. For example, a dendrimer having a disulfide (--S--S--) bond in its core. The final external layer of the dendrimer can be capped with a reactive group

such as an amine or carboxyl group. These reactive groups can then be derivatized with either targeting entities or therapeutic entities (or, in some cases, a mixture of both). The core disulfide bond can then be reduced to a thiol, and the complementary entity attached via the thiol functionality. That is, if a therapeutic entity had been attached to the external layer of the dendrimeric linking carrier, upon reduction and formation of the thiol functionality, a targeting entity can be attached via the free --SH group (paragraph 0120 – 0122).

It would have been further obvious to one of ordinary skill in the art at the time of the invention to substitute a dendrimer having a disulfide bond it in its core in the conjugate of Kobayashi for linking to chelate or polymer when the disclosure of Kobayashi and Domb is taken in view of Danthi. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Danthi teaches that dendrimer having disulfinde in its core can be capped with an amine or carboxyl group for derivatization with therapeutic moieties, as was shown by Kobayashi with functionally equivalent dendrimers.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS